



PATENT APPLICATION
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Fikstad et al.	CERTIFICATE OF DEPOSIT UNDER 37 C.F.R. § 1.8 I hereby certify under 37 CFR § 1.8 that this correspondence is being facsimile transmitted to the USPTO or being deposited with the United States Postal Service with sufficient postage as first class postage in an envelope addressed to Commissioner of Patents PO Box 1450 Alexandria, VA 22313-1450 on the date indicated below. <u>Judy Anderson</u> Name <u>10/31/2007</u> Date of Deposit
SERIAL NO.:	10/700,838	
FILED:	Nov. 3, 2003	
FOR:	PHARMACEUTICAL COMPOSITIONS WITH SYNCHRONIZED SOLUBILIZER RELEASE	
ART UNIT:	1614	
EXAMINER:	Royds, Leslie A	
DOCKET NO.:	01235-23625	

DECLARATION OF CHANDRASHEKAR GILIYAR
UNDER 37 C.F.R. § 1.132

Mail Stop
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Chandrashekar Giliyar declare as follows:

1. I hold a Bachelor's Degree in Pharmacy from the Govt. College of Pharmacy, Bangalore University, India, a Masters in Pharmaceutical Technology from University of Baroda, India, and a Ph.D. in Pharmaceutical Sciences, Mangalore University, India.

2. I have worked extensively in the Pharmaceutical field including working as a Manager of Product Development for GlaxoSmithkline Pharmaceuticals in Bangalore, India, and my current position as a Senior Scientist at Lipocine, Inc.

3. I am a named inventor on several United States patent applications, including United States Patent Application Serial No. 10/700,838 (hereinafter "the '838 application), filed Nov. 3, 2003, which I have recently reviewed.

4. I organized and directed the following experiments related to the solubility of cilostazol in d- α -tocopheryl polyethylene glycol succinate, 7.2:1 w/w mixtures of d- α -tocopheryl polyethylene glycol succinate and d- α -tocopheryl succinate, and 7.2:1 w/w mixtures of d- α -tocopheryl polyethylene glycol succinate and glyceryl monostearate. The experiments as presented in the declaration were conducted to demonstrate the extremely low solubility levels of cilostazol in the claimed formulations of the '838 application, particularly with respect to the formulations exemplified in Example 2. Additionally, the experiments were conducted to demonstrate the inherent teaching that at least about 95% of the cilostazol present in the formulation found in Example 2 of the '838 application is present in a suspended form.

5. The experiment involved the preparation of three different sample compositions using the three solubilizer mixtures, namely: 1) d- α -tocopheryl polyethylene glycol succinate, 2) 7.2:1 w/w mixtures of d- α -tocopheryl polyethylene glycol succinate and d- α -tocopheryl succinate, and 3) 7.2:1 w/w mixtures of d- α -tocopheryl polyethylene glycol succinate and glyceryl monostearate. The exact components used are set forth in the following table:

Component	Lot #	Supplier
Cilostazol (micronized)	947400402	Teva API Division, Israel
d- α -tocopheryl polyethylene glycol succinate, (TPGS)	60014000	Eastman Co, UK
d- α -Tocopheryl succinate (TS)	VT0959	Spectrum Chemical Co., NJ
Glyceryl Monostearate (GMS)	10540401	Stepan, NJ

6. The sample compositions were prepared and tested as follows: (as TPGS and the other component mixtures are solid at room temperature, solubility of the cilostazol can only be tested at elevated temperature ranges) 1) About 10 g each of TPGS; TPGS:TS mixture (7.2:1 ratio by weight) and TPGS:GMS mixture (7.2:1 ratio by weight) were weighed into separate glass scintillation vial, tightly closed and labeled appropriately; 2) All the vials were placed in a water

bath maintained at 75°C, until the contents in all the vials were completely molten and formed homogenous solution; 3) While maintaining the solution in the vials of step 2 at 75°C, about 400 mg of cilostazol (micronized) was added into each of the vials and the lid of the vials was tightly closed; 4) All the vials were immediately attached to a rotor and the whole assembly was placed in an oven maintained at 73°C. The rotor was rotated at 10 rpm for 24 hours; 5) At the end of 24 hours of rotation, a small portable centrifuge was placed in the oven at 73°C. About 1-2 g of the sample from each of the vials of step-5 was transferred to preheated (73°C) centrifuge tubes which were centrifuged at 1200 rpm for 10 minutes on the portable centrifuge; 6) Replicate (n=3) aliquots of the clear supernatant from each of the vials was weighed into tarred 100 mL volumetric flasks. The volume is made up with acetonitrile and shaken well; 7) About 1 mL of the solution from step 8 was transferred into HPLC vials and analyzed for cilostazol by HPLC as per the in-house standard test method ARD-047; 8) The solubility of cilostazol in the components and the mixtures were calculated and presented as mg cilostazol solubilized per g solvent component.

7. The experimental results of cilostazol solubility in TPGS and its separate mixtures with TS and GMS are shown in the following table:

Component/Mixture	Mean Cilostazol Solubility, in mg/g (std. dev, N=3)
TPGS	5.4 (1.4)
TPGS – TS Mixture (7.2:1 ratio by weight)	4.0 (0.9)
TPGS – GMS Mixture (7.2:1 ratio by weight)	4.2 (0.6)

8. The above described experiment and accompanying experimental data demonstrate that the solubility of cilostazol in the different inactive component/solubilizers at about 75° C is only about 0.5% w/w. Accordingly, the solubility of cilostazol in the same compositions at room temperature is likely to be even lower.

9. For the reasons stated above, I believe that the solubility of the cilostazol present in the formulation of Example 2 of the '838 application would be no greater than 0.5% w/w, and hence at least 95 wt% of the cilostazol present would be present in a suspended form.

10. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful, false statement may jeopardize the validity of any reexamination certificate issuing on the above-identified proceeding.

DATED this 31st day of October, 2007.

A handwritten signature in black ink, appearing to read "Chandrashekar", is written over a horizontal line.

Dr. Chandrashekar Giliyar